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Perspectives in Disease Prevention and Health Promotion

Safety of Therapeutic Products Used for Hemophilia Patients

On January 11, 1988, CDC sponsored a meeting in Atlanta, Georgia, for health-care providers and consultants concerned with hemophilia. The purpose of the meeting was to share current epidemiologic and clinical trial data, to address therapeutic issues, and to review the safety of products used for treating hemophilia patients. Participants included CDC attendees; consultants from the Food and Drug Administration, National Institutes of Health, Canadian Federal Centre for AIDS, and other public health agencies; and experts in hemophilia treatment or infectious diseases. This report summarizes information discussed at that meeting concerning the safety of therapeutic products used for treating hemophilia patients, specifically with regard to the transmission of human immunodeficiency virus (HIV) and non-A, non-B hepatitis (NANBH) viruses.

The treatment of hemophilia patients includes the use of manufactured blood components (factor concentrates) that are heat-treated or otherwise treated to reduce the risk of the transmission of infectious agents. The safety provided by various heat-treated products depends upon the heating temperature, the duration of heating, and the moisture content of the product during heating. Other factors unique to the production method for each concentrate may also affect the margin of safety, including the use and nature of stabilizers and other proteins present in the factor VIII preparation.

Human Immunodeficiency Virus

Pools of source plasma used for producing factor concentrates may contain units of plasma that were collected from donors who are infected with HIV but who are HIV-antibody-negative.* However, cases of HIV seroconversion associated with the use of heat-treated products are now rare. Since 1985, CDC has evaluated more than 75 reports, worldwide, of HIV seroconversion possibly associated with heat-treated products. Of these, 18 met CDC's operational criteria for a probable association with heat-treated factor concentrates (Table 1). Fourteen of the 18 patients had received products made by one manufacturing process: heat treatment in the lyophilized state (dry) at 60 °C for 30 hours. Nine additional reports are still under investigation.

*The period between HIV exposure and seroconversion is usually less than 14 weeks (*1*); rarely, it may exceed 6 months (*2*).

Therapeutic Products — Continued

Six seroconversions involved patients without any previous exposure to unheated products or to other blood components from HIV-untested donors; they included four of eight Canadian seroconverters, one of four U.S. patients, and one of six Europeans. The other 12 patients had received at least some earlier treatment with unheated concentrates. For some of these patients, the seroconversions—though considerably delayed—may have been attributable to previous therapy with unheated products.

A review of the products received by the 18 patients during the relevant period defined by the CDC operational criteria indicated that eight patients had received exclusively U.S.-manufactured factor VIII concentrates made from HIV-antibody-negative plasma. These concentrates had been heated in the dry state, in accordance with approved procedures, at 60 °C for either 24 hours or 30 hours.

One of the eight seroconversions occurred in a U.S. patient who had received, during the 10 months before seroconversion, five lots of one U.S. manufacturer's factor VIII concentrate, which had been heated for 24 hours. The patient was being monitored monthly for HIV antibody as part of an immune tolerance induction protocol for factor VIII inhibitor (*3*). The other seven patients whose seroconversions were associated with donor-tested concentrates were residents of Western Canada; their seroconversions were noted during testing in mid-1987.

The Canadian seroconverters had received products from at least two manufacturers. Some of the administered lots (from one manufacturer) had been made from plasma collected before HIV-antibody testing became available. These lots had been heated in the dry state at 68 °C for 72 hours. However, an epidemiologic investigation showed a strong statistical association between seroconversion and receipt of one or more of three lots of heat-treated (60 °C, 30 hours) factor VIII concentrates made by another company from one plasma pool (*4*). All plasma donations to this pool had been tested (ELISA) and found to be negative for HIV antibody. Retrospectively, 11 of the 4,200 donations contained in the pool were from seven donors for whom a subsequent donation was tested (ELISA) and reported to be positive; results of confirmatory tests are not available. These 11 donations were collected between 6 and 16 weeks after the antecedent donations to the pool (CDC, unpublished data). The three lots made from this pool and received by these Western Canadian seroconverters were voluntarily withdrawn from Canadian and U.S. markets by December 1987.

Hepatitis Viruses

Products heated in the lyophilized (dry) state at less than 80 °C, including one heated in an immiscible (N-heptane) solvent suspension, are at higher risk of transmitting NANBH viruses than are most of the newer products (described below). However, estimates of the risk of NANBH virus transmission associated with the newer products are less precise than estimates of the risk associated with older

TABLE 1. CDC operational criteria for probable association of HIV seroconversion with virus-inactivated factor concentrates

1. Confirmation of HIV seropositivity.
2. Confirmation that patient was previously HIV seronegative.
3. Any use of non-virus-inactivated concentrates must have preceded the last seronegative test by at least 6 months.
4. No receipt of other HIV-untested blood components during the relevant time period.
5. No recognized or suspected gaps in therapy records.
6. Patient not known to have practiced high-risk behaviors.

Therapeutic Products — Continued

products. The small number of patients receiving newer products and studied in accordance with criteria such as those proposed by the International Committee on Thrombosis and Hemostasis (ICTH) (*5*) affects the precision. These criteria emphasize that detection of infection will be inaccurate if patients receiving new products have been exposed to NANBH virus through previously received blood products or if they are being tested for transient liver-function abnormalities at irregular or infrequent intervals. The ICTH criteria require that the patients be tested for alanine aminotransferase every 2 weeks for the first 4 months after therapy begins and at months 5 and 6.

The ICTH criteria were met by 26 patients studied prospectively while they were receiving products heated in aqueous solution (pasteurized); none contracted hepatitis (*5*). In another study of 28 patients who met these criteria but received a product heated in the presence of steam, four of 14 unvaccinated patients showed evidence of hepatitis B (HB) infection 8–24 weeks after the first infusion; none of the other 24 showed evidence of NANBH (*6*). In a prospective study of 32 British patients who received concentrates dry-heated at 80 °C for 72 hours, 13 met the ICTH criteria; none contracted hepatitis (J.K. Smith, 1988). The products used in the latter two studies, however, are not available in the United States.

In three other trials meeting the criteria, none of the patients contracted viral hepatitis during follow-up periods of 3–21 months of therapy. In the first two studies, 12–20 patients were treated, respectively, with concentrates exposed to solvent/detergent inactivation with tri-n-butyl phosphate (TNBP)/cholate (M. Horowitz, 1988) or with affinity column-purified products subjected to solvent/detergent inactivation by using TNBP/Triton X-100 (E. Gomperts, 1988). In the third study, 25 previously untreated patients were treated with affinity column-purified products subjected to dry-heat treatment at 60 °C for 30 hours (J. Lusher, 1988) (Table 2).

TABLE 2. Methods of factor purification and viral inactivation for factor VIII concentrates currently available in the United States, July 1988

	Heating Conditions			
Purification Method	**Dry State**	**Solvent Suspension**	**Aqueous**	**Other Treatment Solvent/Detergent**
Non-Affinity Column				
Conditions	68°, 72h	60°, 20h	60°, 10h	TNBP*/Cholate
Company	Cutter	Alpha	Behringwerke†	NYBC,§ (ARC)¶
Product	Koate-HT®	Profilate HP®	Humate P®	Factor VIII-SD®
			60°, 10h	
			Cutter	
			Koate-HS®	
Affinity Column				
Conditions	60°, 30h			TNBP/Triton X-100
Company	Armour			Baxter-Hyland (ARC)
Product	Monoclate®			Hemofil M®

*Tri-n-butyl phosphate.
†Behringwerke pasteurized product distributed by Armour Pharmaceutical.
§New York Blood Center.
¶NYBC product distributed by the American Red Cross.

Therapeutic Products — Continued

Reported by: RS Remis, MD, MV O'Shaughnessy, PhD, Federal Centre for AIDS; Bureau of Biologics, Health Protection Br, Dept of National Health and Welfare; L Poffenroth, MD, Laboratory Centre for Disease Control; Canadian Red Cross Society, Ottawa; C Tsoukas, MD, McGill Univ; Canadian Hemophilia Society, Montreal; GH Growe, MD, Hemophilia Treatment Centre; M Schechter, MD, Univ of British Columbia, Vancouver, Canada. JK Smith, PhD, Churchill Hospital, Oxford, United Kingdom. PM Mannucci, MD, Milan, Italy. SL Dietrick, MD, JW Mosley, MD, Transfusion Safety Study, Univ of Southern California, Los Angeles; E Gomperts, MD, Children's Hospital of Los Angeles, California. JP Scott, MD, Milwaukee, Wisconsin. J Lusher, MD, Detroit, Michigan. K Hoots, MD, Houston, Texas. P Levine, MD, Worcester, Massachusetts. J Bouhasin, MD, St. Louis, Missouri. P Haas, PhD, A Brownstein, MPH, MSW, National Hemophilia Foundation; M Horowitz, PhD, New York, New York. Div of Blood and Blood Products, Center for Biologics Evaluation and Research, Food and Drug Administration. National Heart, Lung, and Blood Institute; National Cancer Institute, National Institutes of Health. Div of Host Factors, Center for Infectious Diseases, CDC.

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TABLE I. Summary — cases of specified notifiable diseases, United States

Disease	29th Week Ending			Cumulative, 29th Week Ending		
	Jul. 23, 1988	Jul. 25, 1987	Median 1983-1987	Jul. 23, 1988	Jul. 25, 1987	Median 1983-1987
Acquired Immunodeficiency Syndrome (AIDS)	832	U *	140	17,714	10,475	4,086
Aseptic meningitis	141	377	300	2,506	3,779	3,223
Encephalitis: Primary (arthropod-borne & unspec)	14	32	32	379	535	535
Post-infectious	1	2	2	65	70	70
Gonorrhea: Civilian	13,917	14,462	18,630	372,984	436,124	473,307
Military	211	367	418	6,819	9,157	11,559
Hepatitis: Type A	428	490	419	13,310	13,812	11,831
Type B	412	602	557	12,012	14,376	13,915
Non A, Non B	56	69	69	1,418	1,784	1,998
Unspecified	29	72	100	1,164	1,754	2,655
Legionellosis	9	26	19	466	509	384
Leprosy	-	7	6	94	108	145
Malaria	29	28	22	423	441	465
Measles: Total†	37	76	69	1,683	2,944	2,084
Indigenous	30	74	52	1,510	2,631	1,834
Imported	7	2	10	173	313	240
Meningococcal infections	33	38	38	1,848	1,864	1,802
Mumps	25	108	56	3,105	9,760	2,250
Pertussis	46	61	60	1,156	1,022	1,124
Rubella (German measles)	2	5	12	130	245	417
Syphilis (Primary & Secondary): Civilian	754	646	580	20,790	18,831	15,313
Military	4	2	5	95	90	110
Toxic Shock syndrome	9	7	7	171	174	217
Tuberculosis	386	484	484	10,975	11,586	11,628
Tularemia	5	6	6	96	98	98
Typhoid Fever	-	13	5	189	168	171
Typhus fever, tick-borne (RMSF)	48	30	46	306	316	342
Rabies, animal	67	101	101	2,335	2,797	2,889

TABLE II. Notifiable diseases of low frequency, United States

	Cum. 1988		Cum. 1988
Anthrax	-	Leptospirosis (La. 1)	18
Botulism: Foodborne (Ore. 2)	13	Plague (Colo. 2)	4
Infant	21	Poliomyelitis, Paralytic	-
Other	3	Psittacosis (Ore. 1)	42
Brucellosis	34	Rabies, human	-
Cholera	-	Tetanus (Tex. 1)	24
Congenital rubella syndrome	3	Trichinosis	38
Congenital syphilis, ages <1 year	171		
Diphtheria	-		

*Because AIDS cases are not received weekly from all reporting areas, comparison of weekly figures may be misleading.
†Seven of the 37 reported cases for this week were imported from a foreign country or can be directly traceable to a known internationally imported case within two generations.

TABLE III. Cases of specified notifiable diseases, United States, weeks ending July 23, 1988 and July 25, 1987 (29th Week)

Reporting Area	AIDS	Aseptic Meningitis	Encephalitis		Gonorrhea (Civilian)		Hepatitis (Viral), by type				Legionellosis	Leprosy
			Primary	Post-infectious			A	B	NA,NB	Unspecified		
	Cum. 1988	Cum. 1988	Cum. 1988	Cum. 1988	Cum. 1988	Cum. 1987	Cum. 1988	Cum. 1988	Cum. 1988	Cum. 1988	Cum. 1988	Cum. 1988
UNITED STATES	17,714	2,506	379	65	372,984	435,124	13,310	12,012	1,418	1,164	466	94
NEW ENGLAND	725	114	13	1	11,082	13,514	501	712	91	63	19	11
Maine	24	7	1	-	231	388	14	30	3	1	2	-
N.H.	19	15	1	-	143	224	31	37	7	3	1	-
Vt.	8	8	3	-	80	116	7	19	5	2	1	-
Mass.	397	44	6	1	3,956	4,904	231	444	61	45	12	10
R.I.	47	29	-	-	1,032	1,124	55	62	9	-	3	1
Conn.	230	11	2	-	5,640	6,758	163	120	6	12	-	-
MID. ATLANTIC	5,953	226	38	4	55,616	71,417	810	1,567	88	131	115	8
Upstate N.Y.	792	126	26	1	7,799	9,328	443	410	40	13	50	-
N.Y. City	3,310	53	7	3	22,853	37,909	170	721	10	92	17	7
N.J.	1,343	47	5	-	8,200	9,062	136	363	29	26	20	1
Pa.	508	-	-	-	16,764	15,118	61	73	9	-	28	-
E.N. CENTRAL	1,251	333	91	7	59,205	63,366	864	1,293	119	61	104	1
Ohio	277	118	28	2	13,568	14,123	194	320	19	10	43	-
Ind.	80	38	11	-	4,605	4,975	77	180	11	15	8	-
Ill.	564	49	19	5	17,468	19,536	240	233	43	13	-	-
Mich.	261	111	23	-	19,136	18,932	213	413	26	20	42	-
Wis.	69	17	10	-	4,428	5,799	140	147	18	3	11	1
W.N. CENTRAL	410	106	25	5	15,178	17,583	785	574	67	19	53	1
Minn.	88	19	2	2	2,062	2,751	58	81	12	3	2	-
Iowa	21	19	8	-	1,166	1,696	33	54	11	1	13	-
Mo.	211	34	1	-	8,584	9,123	448	342	31	9	11	-
N. Dak.	2	-	4	-	84	160	3	3	2	4	1	-
S. Dak.	5	10	1	1	299	320	6	3	2	-	14	-
Nebr.	25	5	4	2	891	1,159	33	32	-	-	5	-
Kans.	58	19	5	-	2,102	2,374	204	59	9	2	7	1
S. ATLANTIC	3,062	600	53	26	110,068	113,952	1,167	2,490	215	163	82	1
Del.	30	11	2	-	1,571	1,758	21	73	6	1	7	-
Md.	328	62	4	3	10,659	12,815	153	383	21	10	11	1
D.C.	291	11	-	1	7,797	7,690	12	27	3	1	-	-
Va.	183	65	20	3	7,396	8,350	254	192	51	105	6	-
W. Va.	9	12	4	-	752	842	8	32	2	3	-	-
N.C.	172	81	14	-	17,322	16,843	190	443	47	-	25	-
S.C.	104	10	-	1	9,505	9,459	29	312	8	3	12	-
Ga.	434	75	1	-	21,003	19,668	217	374	8	3	11	-
Fla.	1,511	273	8	18	34,063	36,527	283	654	69	37	10	-
E.S. CENTRAL	442	182	30	6	29,004	32,705	401	730	102	7	19	1
Ky.	50	55	10	1	2,836	3,227	338	132	37	2	8	-
Tenn.	210	14	6	-	9,739	11,387	40	362	27	-	6	-
Ala.	112	89	14	2	9,166	10,578	8	186	32	5	3	1
Miss.	70	24	-	3	7,263	7,513	15	50	6	-	2	-
W.S. CENTRAL	1,433	306	43	2	42,208	48,459	1,512	993	107	295	12	19
Ark.	52	5	2	-	4,166	5,676	177	60	1	9	2	-
La.	205	56	16	-	8,606	8,898	84	191	16	9	4	1
Okla.	83	25	4	-	3,827	5,426	255	101	25	19	6	-
Tex.	1,093	220	21	2	25,609	29,459	996	641	65	258	-	18
MOUNTAIN	551	96	20	2	8,016	11,444	1,880	941	150	101	25	1
Mont.	9	2	-	-	250	305	23	32	8	3	-	-
Idaho	6	1	-	-	217	404	94	62	4	3	-	-
Wyo.	3	1	-	-	129	264	4	9	3	-	2	-
Colo.	211	35	3	-	1,795	2,464	128	117	42	50	5	1
N. Mex.	26	5	2	-	738	1,250	355	140	11	1	1	-
Ariz.	169	30	6	1	2,850	3,976	938	360	45	27	12	-
Utah	42	13	4	1	317	347	213	84	26	13	2	-
Nev.	85	9	5	-	1,720	2,434	125	137	11	4	3	-
PACIFIC	3,887	543	66	12	42,607	61,685	5,390	2,712	479	324	37	51
Wash.	235	-	3	4	3,494	4,732	1,181	420	96	32	10	3
Oreg.	121	-	-	-	1,755	2,324	827	339	48	13	-	1
Calif.	3,455	481	60	8	36,388	53,203	3,194	1,890	330	270	24	39
Alaska	14	11	2	-	610	920	182	34	4	5	-	1
Hawaii	62	51	1	-	360	506	6	29	1	4	3	7
Guam	1	-	-	-	86	123	5	7	-	2	1	3
P.R.	769	23	2	1	778	1,201	27	153	25	27	-	3
V.I.	25	-	-	-	218	143	1	5	2	-	-	-
Amer. Samoa	-	-	-	-	45	45	-	2	-	4	-	2
C.N.M.I.	-	-	-	-	27	-	1	2	-	4	-	-

N: Not notifiable U: Unavailable C.N.M.I.: Commonwealth of the Northern Mariana Islands

TABLE III. (Cont'd.) Cases of specified notifiable diseases, United States, weeks ending July 23, 1988 and July 25, 1987 (29th Week)

Reporting Area	Malaria	Measles (Rubeola)					Menin-gococcal infections	Mumps		Pertussis			Rubella		
		Indigenous		Imported*		Total									
	Cum. 1988	1988	Cum. 1988	1988	Cum. 1988	Cum. 1987	Cum. 1988	1988	Cum. 1988	1988	Cum. 1988	Cum. 1987	1988	Cum. 1988	Cum. 1987
UNITED STATES	423	30	1,510	7	173	2,944	1,848	25	3,105	48	1,156	1,022	2	130	245
NEW ENGLAND	36	-	80	-	48	250	152	-	98	4	94	35	-	1	1
Maine	2	-	7	-	-	3	7	-	-	-	11	5	-	-	1
N.H.	1	-	66	-	44	151	17	-	94	-	29	4	-	-	-
Vt.	2	-	-	-	-	26	9	-	1	-	2	4	-	-	-
Mass.	19	-	1	-	-	48	67	-	3	-	37	9	-	-	-
R.I.	4	-	-	-	-	2	21	-	-	2	4	1	-	1	-
Conn.	8	-	6	-	4	20	31	-	-	2	11	12	-	-	-
MID. ATLANTIC	56	12	534	1	26	527	179	-	284	6	66	126	1	12	11
Upstate N.Y.	19	1	15	1†	4	34	87	-	69	1	39	95	-	2	9
N.Y. City	27	-	39	-	2	420	46	-	92	-	1	-	1	7	1
N.J.	5	-	2	-	11	35	45	-	31	-	4	6	-	1	1
Pa.	5	11	478	-	9	38	1	-	72	5	21	25	-	2	-
E.N. CENTRAL	37	-	129	-	40	286	248	3	659	1	115	130	1	23	29
Ohio	4	-	2	-	21	5	85	-	96	-	25	35	-	-	-
Ind.[†]	2	-	56	-	-	-	21	-	63	-	55	4	-	-	-
Ill.	1	-	53	-	15	117	50	-	242	-	2	13	1	19	20
Mich.	18	-	18	-	4	29	56	3	173	1	22	28	-	4	9
Wis.	2	-	-	-	-	137	36	-	85	-	11	50	-	-	-
W.N. CENTRAL	11	-	11	-	-	220	70	1	116	2	56	63	-	-	1
Minn.	5	-	10	-	-	36	16	-	-	-	17	10	-	-	-
Iowa	1	-	-	-	-	-	-	-	31	2	18	15	-	-	1
Mo.	3	-	1	-	-	182	24	-	30	-	9	19	-	-	-
N. Dak.	-	-	-	-	-	1	-	-	-	-	6	5	-	-	-
S. Dak.	-	-	-	-	-	-	3	1	1	-	2	2	-	-	-
Nebr.	1	-	-	-	-	-	9	-	11	-	-	1	-	-	-
Kans.	1	-	-	-	-	1	18	-	43	-	4	11	-	-	-
S. ATLANTIC	59	-	254	-	12	113	328	3	475	9	143	181	-	15	13
Del.	-	-	-	-	-	31	1	-	-	1	4	-	-	-	2
Md.	7	-	6	-	2	4	35	-	79	-	26	5	-	-	2
D.C.	7	-	-	-	-	1	7	1	170	-	-	-	-	-	-
Va.	9	-	154	-	2	1	38	-	132	-	27	38	-	11	1
W. Va.	-	-	6	-	-	-	3	-	8	1	4	29	-	-	-
N.C.	10	-	-	-	1	3	55	-	35	4	37	75	-	-	1
S.C.	7	-	-	-	-	-	33	-	4	-	1	-	-	-	-
Ga.	4	-	-	-	-	1	47	-	25	-	20	17	-	1	1
Fla.	15	-	88	-	7	72	109	2	22	3	24	17	-	3	6
E.S. CENTRAL	7	3	48	-	-	2	174	3	371	2	25	22	-	-	3
Ky.	-	3	35	-	-	-	36	-	170	-	-	1	-	-	2
Tenn.	-	-	-	-	-	-	102	2	188	1	13	8	-	-	1
Ala.	4	-	-	-	-	-	25	1	10	1	11	10	-	-	-
Miss.	3	-	13	-	-	2	11	N	N	-	1	5	-	-	-
W.S. CENTRAL	46	-	11	-	3	314	121	6	608	-	72	87	-	7	5
Ark.	1	-	-	-	1	-	16	-	78	-	7	8	-	3	2
La.	8	-	-	-	-	-	37	2	228	-	11	17	-	-	-
Okla.	7	-	8	-	-	2	13	1	164	-	27	62	-	1	-
Tex.	29	-	3	-	2	312	55	3	138	-	27	-	-	3	3
MOUNTAIN	19	-	116	6	10	479	54	-	148	16	357	100	-	5	19
Mont.	2	-	-	6†	8	124	2	-	2	-	1	4	-	-	3
Idaho	-	-	-	-	1	-	5	-	2	1	249	33	-	-	1
Wyo.	-	-	-	-	-	2	-	-	2	-	1	5	-	-	1
Colo.	9	-	116	-	1	5	14	-	28	1	14	27	-	1	-
N. Mex.	1	-	-	-	-	317	10	N	N	2	9	7	-	-	-
Ariz.	4	-	-	-	-	27	13	-	100	12	62	23	-	-	4
Utah	2	-	-	-	-	1	9	-	3	-	20	1	-	3	10
Nev.	1	-	-	-	-	3	1	-	11	-	1	-	-	1	-
PACIFIC	163	15	327	-	34	751	522	9	366	6	229	278	-	67	163
Wash.	9	-	2	-	-	32	45	3	19	2	49	44	-	-	-
Oreg.	9	-	3	-	-	35	28	N	N	2	11	14	-	-	1
Calif.	139	15	320	-	29	680	429	6	320	2	119	113	-	50	101
Alaska	2	-	-	-	-	-	6	-	7	-	5	3	-	-	2
Hawaii	4	-	2	-	5	4	14	-	9	-	45	104	-	17	59
Guam	-	-	-	-	1	2	-	-	2	-	-	-	-	1	1
P.R.	1	-	190	-	-	654	8	-	6	-	9	12	-	1	2
V.I.	-	-	-	-	-	-	-	-	14	-	-	-	-	-	-
Amer. Samoa	-	-	-	-	-	-	2	-	3	-	-	-	-	-	-
C.N.M.I.	1	-	-	-	-	-	1	-	1	-	-	-	-	-	-

*For measles only, imported cases includes both out-of-state and international importations.
N: Not notifiable U: Unavailable †International §Out-of-state

TABLE III. (Cont'd.) Cases of specified notifiable diseases, United States, weeks ending July 23, 1988 and July 25, 1987 (29th Week)

Reporting Area	Syphilis (Civilian) (Primary & Secondary)		Toxic-shock Syndrome	Tuberculosis		Tula-remia	Typhoid Fever	Typhus Fever (Tick-borne) (RMSF)	Rabies, Animal
	Cum. 1988	Cum. 1987	Cum. 1988	Cum. 1988	Cum. 1987	Cum. 1988	Cum. 1988	Cum. 1988	Cum. 1988
UNITED STATES	20,790	18,831	171	10,975	11,586	96	189	306	2,335
NEW ENGLAND	587	316	14	285	359	2	16	8	7
Maine	8	1	3	17	17	-	-	-	1
N.H.	6	3	3	6	8	-	-	-	3
Vt.	2	1	2	2	7	-	1	-	-
Mass.	236	156	6	170	197	1	11	4	-
R.I.	19	8	-	24	30	-	-	2	-
Conn.	316	147	-	66	100	1	4	2	3
MID. ATLANTIC	4,002	3,608	26	1,938	1,956	-	34	12	282
Upstate N.Y.	275	112	11	284	291	-	5	5	16
N.Y. City	2,486	2,623	5	913	937	-	18	5	-
N.J.	480	394	3	355	368	-	11	-	3
Pa.	762	479	7	386	360	-	-	2	263
E.N. CENTRAL	618	491	26	1,244	1,339	1	22	24	78
Ohio	65	56	20	240	255	-	5	19	3
Ind.	34	35	-	124	136	-	2	-	17
Ill.	307	267	-	515	567	-	10	2	16
Mich.	194	95	6	307	321	1	4	2	17
Wis.	18	38	-	58	60	-	1	1	25
W.N. CENTRAL	130	85	21	274	348	49	4	47	283
Minn.	13	11	3	44	73	3	2	2	90
Iowa	15	12	4	24	19	-	-	-	13
Mo.	76	43	7	135	195	30	2	28	10
N. Dak.	1	-	2	5	6	-	-	-	57
S. Dak.	-	8	1	21	17	12	-	6	83
Nebr.	19	7	2	9	12	2	-	1	9
Kans.	6	4	2	36	26	2	-	10	21
S. ATLANTIC	7,852	6,500	14	2,374	2,519	4	20	100	781
Del.	65	47	1	19	25	1	-	-	36
Md.	431	332	2	236	218	-	1	16	190
D.C.	356	186	-	101	79	-	1	-	4
Va.	235	165	-	219	267	2	8	9	226
W. Va.	7	6	-	47	66	-	-	1	63
N.C.	427	358	6	205	260	-	1	50	2
S.C.	431	424	2	273	238	-	-	12	50
Ga.	1,254	881	-	378	436	1	2	9	151
Fla.	4,446	4,103	3	896	930	-	7	3	59
E.S. CENTRAL	1,089	1,075	13	899	985	7	3	36	172
Ky.	37	9	6	222	240	4	1	10	69
Tenn.	489	448	4	255	284	2	-	20	55
Ala.	318	274	3	278	290	-	1	4	48
Miss.	265	344	-	144	171	1	1	2	-
W.S. CENTRAL	2,421	2,381	17	1,452	1,333	23	6	70	322
Ark.	132	156	1	154	162	15	-	11	53
La.	455	406	-	190	144	-	2	-	6
Okla.	88	88	6	139	131	8	-	50	24
Tex.	1,746	1,731	10	969	896	-	4	9	239
MOUNTAIN	379	380	20	278	344	6	6	7	195
Mont.	2	8	-	5	9	-	1	6	130
Idaho	2	3	3	11	21	-	-	1	1
Wyo.	1	1	-	2	1	-	-	-	25
Colo.	62	66	3	27	89	5	3	-	7
N. Mex.	25	31	-	63	54	1	1	-	4
Ariz.	99	176	5	142	139	-	1	-	25
Utah	11	15	9	-	16	-	-	-	3
Nev.	177	81	-	28	15	-	-	-	-
PACIFIC	3,912	3,995	20	2,231	2,403	4	78	2	215
Wash.	98	77	2	122	145	-	5	-	-
Oreg.	163	148	1	80	62	-	6	1	-
Calif.	3,622	3,758	17	1,914	2,048	2	64	1	207
Alaska	8	3	-	26	32	2	-	-	8
Hawaii	21	9	-	89	116	-	3	-	-
Guam	3	2	-	8	25	-	-	-	-
P.R.	340	556	-	105	175	-	4	-	40
V.I.	1	3	-	4	2	-	-	-	-
Amer. Samoa	-	-	-	3	2	-	1	-	-
C.N.M.I.	1	-	-	12	-	-	-	-	-

U: Unavailable

TABLE IV. Deaths in 121 U.S. cities,* week ending July 23, 1988 (29th Week)

Reporting Area	All Causes, By Age (Years)						P&I**
	All Ages	≥65	45-64	25-44	1-24	<1	Total
NEW ENGLAND	643	418	135	64	10	16	56
Boston, Mass.	211	111	55	31	4	10	29
Bridgeport, Conn.	47	32	13	1	-	1	4
Cambridge, Mass.	18	14	3	1	-	-	3
Fall River, Mass.	34	27	5	2	-	-	2
Hartford, Conn.	74	51	14	6	2	1	1
Lowell, Mass.	26	18	6	2	-	-	1
Lynn, Mass.	15	10	3	2	-	-	-
New Bedford, Mass.	21	15	4	1	1	-	-
New Haven, Conn.	47	29	8	5	3	2	5
Providence, R.I.	32	27	3	2	-	-	-
Somerville, Mass.	4	4	-	-	-	-	-
Springfield, Mass.	37	21	7	7	-	2	3
Waterbury, Conn.	22	16	6	-	-	-	2
Worcester, Mass.	55	43	8	4	-	-	6
MID. ATLANTIC	2,785	1,818	522	283	73	88	120
Albany, N.Y.	42	28	4	4	-	6	1
Allentown, Pa.§	13	11	1	1	-	-	-
Buffalo, N.Y.	173	125	27	13	5	3	16
Camden, N.J.	48	31	8	3	3	3	1
Elizabeth, N.J.	15	13	-	2	-	-	1
Erie, Pa.†	37	30	5	1	1	-	4
Jersey City, N.J.	64	42	10	5	3	3	2
N.Y. City, N.Y.	1,389	856	274	186	42	41	47
Newark, N.J.	46	26	7	10	1	2	-
Paterson, N.J.	27	20	3	4	-	-	2
Philadelphia, Pa.	496	326	103	35	10	22	14
Pittsburgh, Pa.†	76	52	13	8	1	2	2
Reading, Pa.	35	30	3	-	1	1	4
Rochester, N.Y.	102	74	19	2	3	4	15
Schenectady, N.Y.	40	26	13	-	1	-	-
Scranton, Pa.†	36	26	6	4	-	-	1
Syracuse, N.Y.	65	46	15	1	2	-	4
Trenton, N.J.	24	17	4	2	-	1	2
Utica, N.Y.	23	20	3	-	-	-	2
Yonkers, N.Y.§	24	19	4	1	-	-	2
E.N. CENTRAL	2,373	1,535	495	180	75	88	95
Akron, Ohio	77	45	20	2	3	7	1
Canton, Ohio	37	24	9	4	-	-	2
Chicago, Ill.§	564	362	125	45	10	22	16
Cincinnati, Ohio	161	110	30	10	6	5	14
Cleveland, Ohio	160	89	38	11	10	12	6
Columbus, Ohio	132	88	28	9	5	2	4
Dayton, Ohio	94	57	23	9	3	2	3
Detroit, Mich.	304	182	63	38	13	8	9
Evansville, Ind.	45	33	10	1	1	-	-
Fort Wayne, Ind.	47	29	10	4	3	1	1
Gary, Ind.	19	13	2	3	-	1	1
Grand Rapids, Mich.	68	49	11	3	1	4	6
Indianapolis, Ind.	169	109	41	6	4	9	3
Madison, Wis.	49	29	7	7	4	2	5
Milwaukee, Wis.	143	101	26	9	1	6	8
Peoria, Ill.	40	28	9	-	2	1	5
Rockford, Ill.	48	29	9	6	3	1	2
South Bend, Ind.	55	37	8	3	2	5	3
Toledo, Ohio	101	78	18	4	1	-	3
Youngstown, Ohio	60	43	8	6	3	-	3
W.N. CENTRAL	771	527	159	42	20	22	31
Des Moines, Iowa	58	39	11	3	4	1	3
Duluth, Minn.	28	22	3	2	-	1	3
Kansas City, Kans.	36	23	5	3	2	3	-
Kansas City, Mo.	128	83	36	5	2	2	3
Lincoln, Nebr.	31	21	8	1	1	-	2
Minneapolis, Minn.	152	108	28	10	2	4	7
Omaha, Nebr.	79	56	17	3	-	3	3
St. Louis, Mo.	126	76	26	12	4	7	6
St. Paul, Minn.	62	47	10	2	3	-	1
Wichita, Kans.§	71	52	15	1	2	1	3
S. ATLANTIC	1,318	770	303	139	47	59	57
Atlanta, Ga.	117	68	23	17	1	8	6
Baltimore, Md.	217	136	56	17	3	5	12
Charlotte, N.C.	121	72	36	8	1	4	12
Jacksonville, Fla.	91	60	15	7	8	1	3
Miami, Fla.	205	85	56	39	11	14	2
Norfolk, Va.	54	34	9	5	3	3	1
Richmond, Va.	88	50	20	7	4	7	7
Savannah, Ga.	76	43	16	6	6	5	3
St. Petersburg, Fla.	59	49	5	3	-	2	3
Tampa, Fla.	61	44	11	1	2	2	4
Washington, D.C.	200	109	47	28	8	8	4
Wilmington, Del.	29	20	9	-	-	-	-
E.S. CENTRAL	800	507	179	73	24	17	39
Birmingham, Ala.	123	74	34	9	3	3	1
Chattanooga, Tenn.	63	49	12	1	1	-	7
Knoxville, Tenn.	97	65	18	10	3	1	4
Louisville, Ky.	72	45	15	7	2	3	3
Memphis, Tenn.	185	111	40	22	6	6	13
Mobile, Ala.	110	77	21	7	3	2	3
Montgomery, Ala.	41	24	10	5	2	-	1
Nashville, Tenn.	109	62	29	12	4	2	7
W.S. CENTRAL	1,341	827	307	106	50	50	51
Austin, Tex.	69	48	12	7	1	1	1
Baton Rouge, La.	47	28	11	2	2	4	-
Corpus Christi, Tex.	72	46	14	6	5	1	-
Dallas, Tex.	205	103	67	18	7	10	5
El Paso, Tex.	57	41	9	4	3	-	6
Fort Worth, Tex	89	63	18	2	3	3	2
Houston, Tex.§	308	176	74	34	13	11	7
Little Rock, Ark.	75	45	18	6	2	3	5
New Orleans, La.	89	58	19	8	3	1	-
San Antonio, Tex.	174	115	36	10	6	7	13
Shreveport, La.	61	42	12	3	3	1	7
Tulsa, Okla.	95	62	17	6	2	8	5
MOUNTAIN	641	378	132	71	36	24	25
Albuquerque, N. Mex.	90	42	16	19	6	7	3
Colo. Springs, Colo.	46	35	9	1	1	-	4
Denver, Colo.	97	54	27	10	5	1	5
Las Vegas, Nev.	81	47	16	11	6	1	3
Ogden, Utah	17	13	3	-	1	-	2
Phoenix, Ariz.	126	75	16	18	8	9	2
Pueblo, Colo.	18	7	8	3	-	-	1
Salt Lake City, Utah	42	25	9	2	1	5	-
Tucson, Ariz.	124	80	28	7	8	1	5
PACIFIC	2,030	1,309	398	197	65	54	104
Berkeley, Calif.	13	9	3	1	-	-	-
Fresno, Calif.	105	63	20	13	4	5	7
Glendale, Calif.§	27	22	5	-	-	-	1
Honolulu, Hawaii	79	51	23	3	-	2	16
Long Beach, Calif.	94	64	17	6	3	4	10
Los Angeles Calif.§	582	395	107	51	17	5	21
Oakland, Calif.	84	46	14	12	8	4	4
Pasadena, Calif.	44	32	8	3	1	-	2
Portland, Oreg.	115	84	11	14	3	3	6
Sacramento, Calif.	140	86	33	13	4	4	7
San Diego, Calif.	131	60	37	22	5	7	9
San Francisco, Calif.	158	90	29	26	6	7	1
San Jose, Calif.	204	144	40	12	6	2	15
Seattle, Wash.	164	97	38	18	4	9	-
Spokane, Wash.	55	41	8	3	2	1	5
Tacoma, Wash.	35	25	5	2	2	1	-
TOTAL	12,702††	8,089	2,630	1,154	400	418	578

*Mortality data in this table are voluntarily reported from 121 cities in the United states, most of which have populations of 100,000 or more. A death is reported by the place of its occurrence and by the week that the death certificate was filed. Fetal deaths are not included.

**Pneumonia and influenza.

†Because of changes in reporting methods in these 3 Pennsylvania cities, these numbers are partial counts for the current week. Complete counts will be available in 4 to 6 weeks.

††Total includes unknown ages.

§Data not available. Figures are estimates based on average of past available 4 weeks.

Therapeutic Products — Continued

Editorial Note: Epidemiologic and laboratory data indicate that processed plasma derivatives currently available in North America, Europe, and Australia have a high degree of safety with regard to HIV transmission (*7*). The data on *in-vitro* inactivation of HIV purposely inoculated (in laboratory culture systems) into factor concentrates (*8–10*) must be supplemented by surveillance for seroconversions in recipients of factor concentrates. Seroconversion data provided to CDC come from a combination of prospective surveillance, ongoing cohort studies, and anecdotal reports. However, concerns regarding these sources of information include: 1) the completeness of surveillance systems, 2) the representativeness of specific cohort studies, and 3) the numbers of seronegative patients who receive each type of virus-inactivated product reportedly associated with seroconversions. Any seroconversion reported to CDC is thoroughly investigated to rule out the following: 1) a source of infection other than receipt of virus-inactivated concentrates, 2) flaws in the manufacturing processes, and 3) errors in donor screening or in HIV-antibody testing procedures.

Estimates for the annual rate of HIV seroconversions associated with donor-screened, virus-inactivated, clotting-factor products have been based on data from several sources, including the National Cancer Institute-coordinated multicenter study, the Transfusion Safety Study, the National Hemophilia Foundation (NHF)/Food and Drug Administration collaborative project, and CDC projects and surveillance. With the products now in use (Table 2), the annual rate appears to be less than one per 1,000. For example, of 1,489 seronegative, predominantly European patients followed through CDC-coordinated surveillance (*11*), none have seroconverted even though, collectively, they have received approximately 75 million units of American- or European-manufactured, virus-inactivated, donor-tested factor concentrates during the past 2½ years (*12*). The proportion of products treated according to more rigorous procedures was higher for these 1,489 patients than the proportion typically received by U.S. and Canadian patients during the same period.

The inactivation of HB and NANBH viruses in factor concentrates has been less satisfactory than that of HIV. The potential for the newer types of factor concentrates to transmit hepatitis viruses is still being studied. Anecdotal cases are often more difficult to evaluate than prospectively studied patients. NANBH reportedly has been associated with concentrates heated in the lyophilized (dry) state at 60 °C for 72 hours (*13*), at 68 °C for 72 hours (*14*), and at 60 °C for 20 hours in a solvent suspension (*15*). Encouraging developments (*16–19*) include newer processes for reducing or eliminating contaminating viruses, for enhancing the purification of clotting factors from source plasma, for increasing viral inactivation, and for developing practical methods for manufacturing factor VIII through recombinant DNA techniques. Compared with older processes, most of the newer processes produce fewer units of factor activity per unit of source plasma collected. Pending procedural improvements, this less efficient recovery of clotting factor reduces the supply of available concentrates.

Presently, the only U.S. product for which dry heating is the primary method of virus inactivation is one heated at 68 °C for 72 hours. The average annual cost of therapy with the newer products represents a threefold increase compared with the cost of the formerly widely used materials treated with dry heat (*17*).

After reviewing the data presented at the CDC-sponsored meeting, the Medical and Scientific Advisory Committee of the NHF established and published recommendations for U.S. physicians treating hemophilia patients. The Committee addressed the following points regarding currently available concentrates (*20*):

Therapeutic Products — Continued

Summary of Recommendations for Physicians Treating Patients with Hemophilia
National Hemophilia Foundation

A. General Recommendations

The risks of withholding factor treatment far outweigh the risks of treatment, but health-care providers should educate patients to use appropriate doses of clotting factor to minimize overuse and to contain costs.

B. For Patients with Factor VIII Deficiency

Desmopressin (DDAVP®) should be used whenever possible by patients with mild or moderate hemophilia A. When feasible, an alternative to concentrates may be the use of cryoprecipitate prepared from one well-screened and repeatedly tested donor or from a small number of such donors.

1. *Prevention of HIV.* Products that are heated in aqueous solution (pasteurized), treated with solvent/detergent, purified with monoclonal antibody, heated in suspension in organic media, or dry heated at high temperatures for long periods are preferred. These products are at substantially reduced risk of transmitting HIV.
2. *Prevention of Hepatitis.* HB vaccination is essential for uninfected patients with hemophilia. Preliminary data suggest that products that are heated in aqueous solution (pasteurized), solvent/detergent treated, or monoclonal-antibody purified are at reduced risk of transmitting hepatitis viruses.

C. For Patients with Factor IX Deficiency

For patients with *severe* factor IX deficiency, NHF continues to recommend the use of virus-inactivated factor IX concentrate. For patients with *mild* or *moderate* factor IX deficiency, when feasible, an alternative would be the use of fresh, frozen plasma prepared from one well-screened and repeatedly tested donor or from a small number of such donors.

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6-20. Available upon request. Contact Dale N. Lawrence, M.D., Division of Host Factors, Center for Infectious Diseases, Mailstop D02, CDC, Atlanta, GA 30333.

Scombroid Fish Poisoning – New Mexico, 1987

In July 1987, state and local public health officials in New Mexico investigated two cases of scombroid fish poisoning (histamine poisoning) in persons living in Albuquerque. The New Mexico Health and Environment Department was initially consulted by an Albuquerque physician regarding two patients, a husband and wife, who had become ill within 45 minutes after eating dinner. Their symptoms included nausea, vomiting, diarrhea, headache, fever, flushing, and rapid pulse rate. An investigation by the Albuquerque Environmental Health Department found that the couple had shared a meal of grilled mahi mahi, pasta, salad, water, and wine. Their dog had eaten some of the fish and had vomited; however, their daughter, who had eaten no fish, did not become ill. Both of the patients had been treated with Benadryl®, activated charcoal, and ipecac in a hospital emergency room. Their symptoms resolved within 36 hours of onset of illness.

Samples of the remaining mahi mahi were sent to the Food and Drug Administration laboratory in Seattle. Histamine was detected in the samples at a ratio of 20 mg/100 g, a level sufficient to cause symptoms (*1*). Samples from a different shipment of fish were obtained from the store in Albuquerque where the mahi mahi was purchased. These samples yielded histamine levels of 3 mg/100 g of sample and were negative for ciguatera toxin.

The fish had been imported from Taiwan through California and shipped frozen to the Albuquerque distributor, where it was thawed and sold from iced refrigerator cases. The patients had frozen the fish after they bought it. Later, they thawed it for 3 hours at room temperature and then grilled the still icy fish.

Reported by: NB Rieder, MD; NI Goertz, RS, JD Hall, DrPH, Albuquerque Environmental Health Dept; M Eidson, DVM, HF Hull, MD, State Epidemiologist, New Mexico Health and Environment Dept. Albuquerque Resident Post, Food and Drug Administration. Enteric Diseases Br, Div of Bacterial Diseases, Center for Infectious Diseases, CDC.

Editorial Note: Of all varieties of fish, the scombroid species (tuna, bonito, and mackerel) and certain other dark-meat fish, such as mahi mahi, are the most likely to develop high levels of histamine. When fresh scombroid fish are not continuously iced or refrigerated, bacteria may convert the amino acid histidine, which occurs naturally in the muscle of the fish, to histamine. Since histamine is resistant to heat, cooking the fish generally will not prevent illness. Histamine levels may not be correlated with any obvious signs of decomposition of the fish. Thus, prompt and proper refrigeration or icing from the time the fish is caught until it is preserved, processed, or cooked is essential to prevent scombroid fish poisoning. Antihistamines may be useful for symptomatic treatment.

Because histamine is metabolized by intestinal flora, even large doses of ingested pure histamine usually do not cause symptoms. Thus, although histamine is a marker for fish that could cause scombroid fish poisoning, the actual mechanism for the poisoning must depend on an additional cofactor. Experimental evidence indicates that other substances produced in fish by putrefactive bacteria inhibit the metabolism of histamine and permit its absorption and circulation (*2*).

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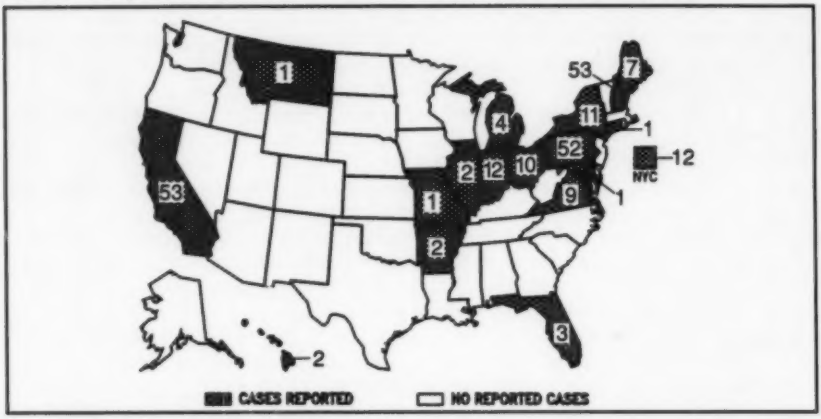
FIGURE I. Reported measles cases — United States, Weeks 25–28, 1988



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The data in this report are provisional, based on weekly reports to CDC by state health departments. The reporting week concludes at close of business on Friday; compiled data on a national basis are officially released to the public on the succeeding Friday. The editor welcomes accounts of interesting cases, outbreaks, environmental hazards, or other public health problems of current interest to health officials. Such reports and any other matters pertaining to editorial or other textual considerations should be addressed to: Editor, *Morbidity and Mortality Weekly Report*, Centers for Disease Control, Atlanta, Georgia 30333.

Director, Centers for Disease Control
James O. Mason, M.D., Dr.P.H.

Editor
Michael B. Gregg, M.D.

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